

VISIT...

LANZAROTE
Caliente.COM

IBOGAINE, an alkaloid found in the root bark of the African shrub *Tabernanthe iboga*, has been claimed to interrupt opioid dependence in humans; in animals, it has been shown to inhibit morphine self-administration and to attenuate signs of morphine withdrawal. However, ibogaine has some neurotoxicity, and because of this, efficacious and safer congeners of ibogaine have been sought. 18-Methoxycoronaridine (18-MC), a novel iboga alkaloid congener, has been shown, in animals, to mimic the effects of ibogaine on morphine self-administration without producing any ibogaine-like neurotoxicity. In the present study, 18-MC was shown to attenuate five of seven signs of morphine withdrawal in rats. The data suggest that 18-MC will ameliorate symptoms of opioid dependence in humans. *NeuroReport* 9: 1283–1285 © 1998 Rapid Science Ltd.

Key words: Drug dependence; Ibogaine; 18-Methoxycoronaridine; Morphine; Opioid

Effects of 18-methoxycoronaridine on acute signs of morphine withdrawal in rats

Brian Rho and Stanley D. Glick^{CA}

Department of Pharmacology and Neuroscience (A-136), Albany Medical College, 47 New Scotland Avenue, Albany, NY 12208, USA

^{CA}Corresponding Author

Introduction

Ibogaine, an alkaloid found in the root bark of the African shrub *Tabernanthe iboga*, has been claimed to interrupt the physiological and psychological aspects of the opiate addiction syndrome (H. Lotsof, U.S. patent number 4,499,096) and to suppress the multiple symptoms and physical discomfort of narcotic withdrawal (ENDABUSETM product information). Consistent with these claims, preclinical studies in animals have shown that ibogaine reduces morphine self-administration and attenuates signs of morphine withdrawal.^{1,2} However, ibogaine has stimulant, hallucinogenic and motor side effects that may limit its therapeutic utility. In rats, whole body tremors are prominent. Such tremors appear to be due to activation of an olivo-cerebellar pathway;^{3–5} at high doses, ibogaine overstimulates this pathway and damages Purkinje cells in the cerebellar vermis.^{5,6} 18-Methoxycoronaridine (18-MC), a synthetic congener of ibogaine, has been developed with the goal of making available a safer ibogaine-like agent. In previous work, 18-MC was shown to mimic the efficacy of ibogaine in inhibiting morphine self-administration while, even at high doses, inducing neither tremors nor cerebellar toxicity.⁷ In the present study we showed that 18-MC attenuates signs of morphine withdrawal in physically dependent rats.

Materials and Methods

The subjects were naïve female Sprague–Dawley (Taconic, Germantown, NY) rats, weighing ~250 g at the beginning of the experiment. The rats were housed in groups of four and maintained on a 12:12 h light:dark cycle.

Morphine was administered s.c. twice a day (09.00 and 15.00 h) for 7 days. The morning and afternoon doses were, respectively, 10 and 20 mg/kg on the first day, 40 and 60 mg/kg on the second day, and 60 and 80 mg/kg on the third and subsequent days. On the withdrawal day (day 8), an injection of 18-MC hydrochloride (10, 20 or 40 mg/kg, i.p.) or saline was followed 30 min later by an injection of naltrexone hydrochloride (1 mg/kg, i.p.). Naltrexone precipitated an immediate withdrawal syndrome which was observed continuously for 2 h. Rats were weighed twice: immediately prior to injection of naltrexone and 2 h later. Other signs of withdrawal (wet-dog shakes, grooming, teeth chattering, flinching, burying and diarrhea) were counted and recorded as the number of incidents of each behavior for each animal. Two rats, one from each of two groups, were observed simultaneously; observations were made blindly without knowledge of which rat received which treatment.

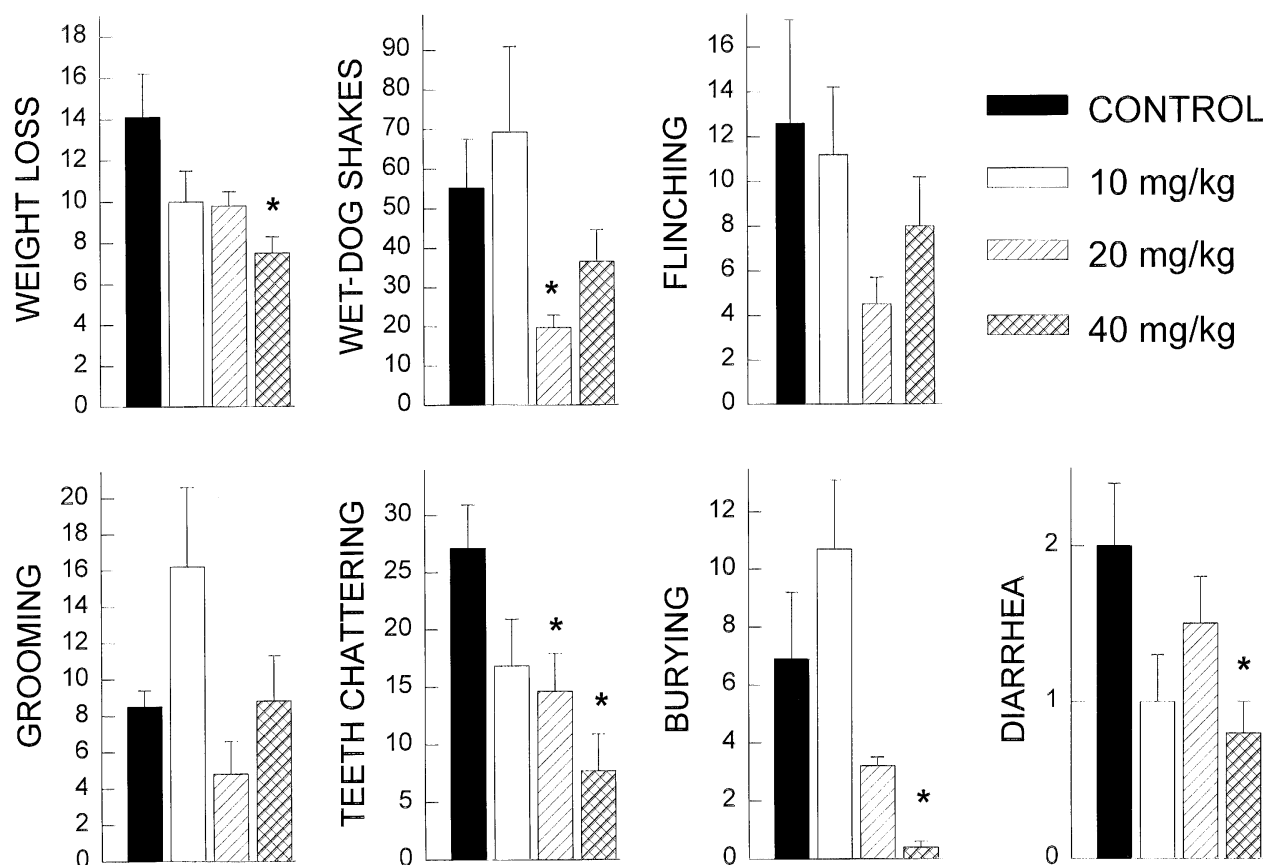


FIG. 1. Effects of 18-MC (10 mg/kg, $n = 6$; 20 mg/kg, $n = 6$; 40 mg/kg, $n = 8$) on withdrawal signs. 18-MC or saline ($n = 8$) was administered 30 minutes before naltrexone (1 mg/kg); withdrawal signs were recorded over the following 2 h. Each value is the mean $\pm$ s.e.m. occurrences of signs (weight loss in g). Asterisks indicate significant differences between 18-MC and saline ($p < 0.05$, ANOVA and Newman-Keuls tests).

Results

The data (Fig. 1) were subjected to a two-way ANOVA with group and sign as the two factors. The analysis showed a significant ($p < 0.05$) effect of group and a significant group $\times$ sign interaction. One-way ANOVAs for each sign showed significant group effects for weight loss, wet-dog shakes, teeth chattering, burying and diarrhea. *Post-hoc* tests (Newman-Keuls) showed significant ($p < 0.05$) effects of 40 mg/kg 18-MC on weight loss, teeth chattering, burying and diarrhea, and significant ($p < 0.05$) effects of 20 mg/kg 18-MC on wet-dog shakes and teeth chattering.

Discussion

18-MC significantly attenuated several signs of opioid withdrawal. The effects of 18-MC were similar though not identical to those of ibogaine reported in a previous study from this laboratory.² While ibogaine decreased grooming and had no effect on weight loss and burying, 18-MC had no effect on

grooming but decreased weight loss and burying. Both ibogaine and 18-MC decreased teeth chattering, wet-dog shakes and diarrhea and neither drug affected flinching. The somewhat different efficacies of 18-MC and ibogaine may be more attributable to the different durations (4 *vs* 7 days) and modes (s.c. implanted silicone reservoir *vs* s.c. injections) of morphine administration in the two studies than to any fundamental difference in the mechanisms of action of ibogaine and 18-MC. In this regard it is noteworthy that weight loss and wet-dog shakes are probably the two most objective and reliable signs of withdrawal, and both were affected by 18-MC. The data suggest that 18-MC should be at least as efficacious as ibogaine in ameliorating symptoms of opioid dependence in humans.

Conclusion

A previous study showed that 18-MC, a novel iboga alkaloid congener, reduces morphine self-administration and is non-toxic.⁷ In the present study 18-MC attenuated five of seven signs of morphine

withdrawal. Considered together, the data from these studies indicate that 18-MC warrants further development as a potential treatment for opioid addiction and dependence.

References

1. Glick SD, Rossman K, Steindorf S and Carlson JN. *Eur J Pharmacol* **195**, 341–345 (1991).
2. Glick SD, Rossman K, Rao NC, Maisonneuve IM and Carlson JN. *Neuropharmacology* **31**, 497–500 (1992).
3. de Montigny C and Lamarre Y. *Brain Res* **53**, 81–95 (1973).
4. Llinas R, and Volkind RA. *Exp Brain Res* **18**, 69–87 (1973).
5. O'Hearn E and Molliver ME. *Neuroscience* **55**, 303–310 (1993).
6. O'Hearn E, Long DB and Molliver ME. *NeuroReport* **4**, 299–302 (1993).
7. Glick SD, Kuehne ME, Maisonneuve IM *et al.* *Brain Res* **719**, 29–35 (1996).

ACKNOWLEDGEMENTS. This work was supported by NIDA Grant #DA03817 and by Albany Molecular Research, Inc.

**Received 27 January 1998;
accepted 15 February 1998**